DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Hanna Zyruk
Director Regulatory Affairs
Iroko Pharmaceuticals, LLC
Navy Yard Corporate Center
One Crescent Drive
Philadelphia, PA 19112

RE: NDA 18-332
INDOCIN® (indomethacin) ORAL SUSPENSION
MACMIS # 18005

Dear Ms. Zyruk:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a dosing sheet (IND0045FC1008) for INDOCIN® (indomethacin) ORAL SUSPENSION (Indocin OS) submitted by Iroko Pharmaceuticals, LLC (Iroko) under cover of Form FDA-2253. The dosing sheet is false or misleading because it omits important risks associated with Indocin OS and omits other material facts associated with the use of the drug. The dosing sheet therefore misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) and 321(n). *Cf*. 21 CFR 202.1(e)(3)(i) & (e)(5).

Background

According to its FDA-approved product labeling (PI), Indocin OS is indicated in the active stages of the following:

1. Moderate to severe rheumatoid arthritis including acute flares of chronic disease.
2. Moderate to severe ankylosing spondylitis.
3. Moderate to severe osteoarthritis.
4. Acute painful shoulder (bursitis and/or tendinitis).
5. Acute gouty arthritis.

The Indications and Usage section of the PI also advises prescribers to "[c]arefully consider the potential benefits and risks of INDOCIN and other treatment options before deciding to use INDOCIN. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. . . ."

The PI includes the following boxed warning for Indocin OS (bolded emphasis in original; underlined emphasis added):

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. . . .

- INDOCIN is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. . . .

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. . . . .

Indocin OS is associated with a number of other serious risks, as reflected in its PI. For example, Indocin OS is contraindicated in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely **fatal** anaphylactic-like reactions to NSAIDs have been reported in such patients. Other serious warnings associated with Indocin OS use include the following: hypertension; congestive heart failure and edema; renal effects; potentially fatal skin reactions; and premature closure of the ductus arteriosus if used in late pregnancy. The PI for Indocin OS also includes information pertaining to serious drug interactions and common adverse reactions.

Additionally, the PI includes detailed dosing and administration instructions for Indocin OS. According to the Dosage and Administration section of the PI (bolded emphasis in original; underlined emphasis added):

> Carefully consider the potential benefits and risks of INDOCIN and other treatment options before deciding to use INDOCIN. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals . . . .
>
> After observing the response to initial therapy with INDOCIN, the dose and frequency should be adjusted to suit an individual patient's needs.
> . . . .
>
> Adverse reactions appear to correlate with the size of the dose of INDOCIN in most patients but not all. Therefore, every effort should be made to determine the smallest effective dosage for the individual patient.

Pediatric Use

INDOCIN ordinarily should not be prescribed for pediatric patients 14 years of age and under . . . .

Adult Use

Dosage Recommendations for Active Stages of the Following:

1. Moderate to severe rheumatoid arthritis . . .
INDOCIN 25 mg (5 mL) b.i.d. or t.i.d. If this is well tolerated, increase the daily dosage by 25 mg (5 mL) or by 50 mg (10 mL), if required by continuing symptoms, at weekly intervals until a satisfactory response is obtained or until a total daily dose of 150-200 mg (30 – 40 mL) is reached. DOSES ABOVE THIS AMOUNT GENERALLY DO NOT INCREASE THE EFFECTIVENESS OF THE DRUG. . . .

In acute flares of chronic rheumatoid arthritis, it may be necessary to increase the dosage by 25 mg (5 mL) or, if required, by 50 mg (10 mL) daily.

If minor adverse effects develop as the dosage is increased, reduce the dosage rapidly to a tolerated dose and OBSERVE THE PATIENT CLOSELY.

If severe adverse reactions occur, STOP THE DRUG. After the acute phase of the disease is under control, an attempt to reduce the daily dose should be made repeatedly until the patient is receiving the smallest effective dose or the drug is discontinued.

Careful instructions to, and observations of, the individual patient are essential to the prevention of serious, irreversible, including fatal, adverse reactions.

As advancing years appear to increase the possibility of adverse reactions, INDOCIN should be used with greater care in the elderly. . . .

2. Acute painful shoulder (bursitis and/or tendinitis).
Initial Dose:
75-150 mg (15 - 30 mL) daily in 3 or 4 divided doses.
The drug should be discontinued after the signs and symptoms of inflammation have been controlled for several days. The usual course of therapy is 7-14 days.

3. Acute gouty arthritis.
Suggested Dose:
INDOCIN 50 mg (10 mL) t.i.d. until pain is tolerable. The dose should then be rapidly reduced to complete cessation of the drug. . . .

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. Although the dosing sheet includes information from the boxed warning for Indocin OS, it fails to include any other risk information for Indocin OS, including information about other serious and potentially **fatal** risks associated with the drug. By omitting this risk information, the dosing sheet misleadingly suggests that Indocin OS is safer than has been demonstrated. We note the statement, "Please see accompanying full Prescribing Information," at the bottom of the dosing sheet; however this does not mitigate this misleading omission of risk information.

Omission of Material Facts

The dosing sheet presents a chart with the five indications for Indocin OS in conjunction with corresponding dosage information for each indication. However, the dosing sheet omits important material facts regarding dosing and administration information for Indocin OS from its PI (see Background section above). As stated above, the PI for Indocin OS contains detailed and important dosing and administration instructions that ". . . are essential to the prevention of serious, irreversible, including **fatal**, adverse reactions" (emphasis added). For example, the PI contains pertinent information such as instructions to use the lowest effective dose for the shortest duration for each individual patient and to slowly increase the dose, as well as information on duration of therapy, and the necessity of carefully monitoring patients and reducing the dose or discontinuing treatment in the event of adverse reactions.

Conclusion and Requested Action

For the reasons discussed above, the dosing sheet misbrands Indocin OS in violation of the Act, 21 U.S.C. 352(a) and 321(n). *Cf*. 21 CFR 202.1(3)(i) & (e)(5).

DDMAC requests that Iroko immediately cease the dissemination of violative promotional materials for Indocin OS such as those described above. Please submit a written response to this letter on or before December 2, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Indocin OS that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to Macmis 18005 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Indocin OS comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Mathilda Fienkeng, Pharm.D.
Regulatory Review Officer,
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-18332	ORIG-1	IROKO PHARMACEUTICALS LLC	INDOCIN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATHILDA K FIENKENG
11/17/2009